Genetic Risk Factors for Placental Abruption

A HuGE Review and Meta-Analysis

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Background: Although the precise pathophysiology that leads to placental abruption is unknown, there is evidence supporting a genetic etiology.

Methods: We searched PubMed and systematically reviewed all case-control studies that investigated the association between genetic variants and placental abruption. Pooled genetic risks were estimated using fixed and random effects odds ratios.

Results: Twenty-two articles, examining a total of 14 gene polymorphisms were identified. Seven polymorphisms (*F5 Arg506Gln, F5 Met385Thr, F2 G20210A, MTHFR A1298C, MTHFD1 Arg653Gln, NOS3 Glu298Asp, AGT Met235Thr*) show significant association in individual studies. Six of the 7 (all except *F5Met385Thr*) were studied more than once and we therefore included them in our meta-analyses. A positive association under the dominant model was found for the *F5 Arg506Gln* and *F2 G20210A* polymorphisms. The random-effects odds ratio for the *F5 Arg506Gln* polymorphism was 3.4 (95% confidence interval = 1.4–8.3) and the fixed-effects odds ratio for the *F2 G20210A* polymorphism was 6.7 (3.2–13).

Conclusion: Considering the multifactorial etiology of abruption and the relatively small numbers of studies and participants, this review provides only the first clues of possible genetic causes. Larger case-control studies that include gene-gene and gene-environment interactions may help to elucidate the genetics of placental abruption further.

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Placental abruption is a dangerous obstetric condition in which the placenta separates prematurely from the uterus.[1] The classic signs and symptoms of placental abruption include vaginal bleeding, back pain, fetal distress, and hypertonic uterus or tetanic contractions.[2,3] The diagnosis of abruption is clinical, with ultrasonography and other tests being of limited value.[4] Placental abruption complicates about 1% of deliveries.[5–9] Perinatal mortality in the United States is about 120 per 1000 births complicated with abruption, compared with 8.2 per 1000 other births.[5] Approximately 25%–30% of fetal and neonatal deaths are associated with placental abruption.[10] Risk factors include abruption in a prior pregnancy, multiparity, advanced maternal age, maternal hypertensive disorders, polyhydramnios, chorioamnionitis, premature rupture of membranes, uterine leiomyomas, cocaine and tobacco use, poor nutrition, trauma, and possibly thrombophilias.[10–20]

The high recurrence rate of placental abruption[21–24] and the high prevalence of thrombophilia among women with abruption[25,26] support the possibility of a genetic contribution to risk. Moreover, abruption risk appears higher in families having an index patient with recurrent placental abruption.[27] Genetic studies involving candidate genes have led to inconsistent results. We searched the literature for genetic studies on associations of genetic variation with risk of developing placental abruption.

METHODS

Selection of Studies

We searched PubMed for all English-language articles published up to September 2007 related to placental abruption and genetic polymorphisms. We used combinations of the following terms as search criteria: "placental abruption," "abruptio placentae," "polymorphism," "gene variant," "genetic variant," "susceptibility," "genetic association study." Bibliographies in articles provided further references.

Our review comprised human genetic association studies fulfilling the following inclusion criteria: (1) cases with clinically diagnosed placental abruption and controls free of placental abruption, (2) information on genotype frequency or risk estimates, and (3) validated molecular methods for genotyping. We focused on case-control genetic association studies investigating susceptibility to placental abruption. Case reports, editorials, and review articles were excluded.

Data Extraction

The following information was extracted for each study: first author, journal, year of publication, ethnicity of study population, demographic characteristics, definition of cases and controls, matching criteria, genotyping procedure,

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presence or absence of masked genotyping, validity of genotyping method, and number of cases and controls for each genotype. The frequencies of the alleles and the genotypic distributions were extracted or calculated, for both cases and controls. Two investigators independently extracted data, discussed all disagreements, and reached consensus on all items.

Data Synthesis

The associations are indicated as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). When more than 1 study investigated the same polymorphism, we carried out a meta-analysis of published results. The meta-analysis examined the overall association in a dominant model for the allele of interest. In the case of a polymorphism with 2 alleles (*A* and *a*), the dominant model is defined as: $aa + Aa$ versus *AA*.[28,29] Pooled ORs were estimated from the individual ORs in the individual studies. Heterogeneity among studies was tested using the Q-statistic (a weighted sum of squares of the deviations of individual study OR estimates from the overall pooled estimate).[30,31] If $P < 0.10$, then heterogeneity was considered statistically significant. Heterogeneity was further quantified with the I^2 metric, which is independent of the number of studies in the meta-analysis. I^2 ranges from 0% to 100%, with higher values denoting greater heterogeneity.[32,33] The pooled OR was estimated using fixed-effects (Mantel-Haenszel) and random-effects (DerSimonian and Laird) models.[34] Random-effects modeling assumes a genuine diversity in the results of various studies, and incorporates a between-study variance. When there is heterogeneity between studies, it is preferable to estimate the pooled OR using the random-effects model.[35] Analyses were performed using Meta-Analyst (Joseph Lau, Tufts-New England Medical Center) and Compaq Visual Fortran90 with the International Mathematics and Statistics Library (IMSL).[35–37]

RESULTS

We identified 1931 articles in PubMed that met the search criteria. The abstracts were independently assessed by 2 investigators for appropriateness for this review. Results were compared and disagreements resolved by consensus. Thirty-four were identified as potentially eligible; the full articles were then evaluated using the inclusion criteria. Data from 22 article[38–59] describing 42 studies met the inclusion criteria; these were included in our review. The diagnostic criteria were similar in the reviewed studies, although not standardized (Table 1). Overall, 10 candidate genes and 14 polymorphisms had been investigated in association with placental abruption (Table 2).

Table 1 presents the study characteristics and the associations between the various polymorphisms and risk of placental abruption. Table 2 shows gene polymorphism characteristics. Table 3 provides the meta-analyses results. Seven polymorphisms (*F5 Arg506Gln, F5 Met385Thr, F2 G20210A, MTHFR A1298C, MTHFD1 Arg653Gln, NOS3 Glu298Asp, AGT Met235Thr*) had statistically significant associations with abruption.[38–40,42–44,46,48,50,52,55,57] The genotype distribution in control subjects was in Hardy-Weinberg equilibrium in 32 studies, while in 8 studies this information was not provided. The genotyping personnel were reported to be masked to phenotype in 3 studies[53,58,59] and the reliability of the genotyping procedure was controlled only in 1 study.[54]

A meta-analysis was performed for polymorphisms *F5 Arg506Gln*,[38,39,41,44–48,53,57] *F2 G20210A*,[39–41,44–46,57] *MTHFR A1298C*,[42,50,59] *MTHFR C677T*,[39,41,42,45,50,54,56,57,59] *NOS3 Glu298Asp*[43,51,52] and *AGT Met235Thr*.[52,55] In the meta-analyses, we used unadjusted risk effects estimates because only 2 studies[58,59] provided ORs adjusted for confounders. Two polymorphisms (*F5 Arg506Gln, F2 G20210A,*) were positively associated with placental abruption in the meta-analyses, although heterogeneity was present for *F5 Arg506Gln* under the dominant model. The results for individual meta-analyses are described below.

Candidate Genes and Biologic Mechanisms

Genes studied in relation to placental abruption (Table 2) are of low penetrance; ie, the probability is relatively low that a woman carrying the allelic variant will present clinical manifestations. Candidate susceptibility genes can be identified by studying the biochemical or physiological pathways that may be involved in placental abruption.

During placental development in normal early pregnancy, spiral artery endothelium is replaced by trophoblast cells. The trophoblast is thereafter incorporated into the arterial wall, which loses its normal histologic characteristics. These changes free the vessels from vasomotor control, allowing vasodilatation and creating a low-resistance vascular bed.[70] In placental abruption, this physiologic change in the blood vessel may not occur, and signs of vasculopathy (eg, atherosclerosis, narrowing, necrosis, and thrombosis) can be seen.[71,72] Hence, genes involved in thrombophilia and hemodynamic changes of pregnancy are candidates for predisposition to placental abruption. Moreover, on the basis of the previously reported associations between placental abnormalities (such as preeclampsia and miscarriages) and oxidative stress genes,[73,74] this group of genes is also a logical candidate.

The candidate genes in abruption studies to date can be classified into 3 main categories: those related to thrombophilia, to hemodynamics, and to oxidative stress. Eight of the polymorphisms in our review have functions reported in the literature (Table 2). In the 6 others, the polymorphisms were not functional (*MTHFD1 Arg653Gln, MTRR A66G, BHMT G742A, F5 Arg485Lys, F5 Met385Thr, THBD Ala455Val*), although even nonfunctional polymorphisms are likely to be in linkage disequilibrium with causative alleles.[75] Table 2 provides the reference Single Nucleotide Polymorphism (SNP) identification (ID) numbers (rs numbers) from the database of

TABLE 1. Studies of Genetic Polymorphisms and Placental Abruption

First Author, Year	Study Area, Ethnicity	Study Population	Placental Abruption Diagnostic Criteria*	Gene (Polymorphism)	Genotype Distribution mtmt/mtwt/wtwt	Showing Association	Comparison	OR (95% CI)	HWE
Wiener-Megnagi, 1998[38]	Israel, mixed	27 cases, (29.5 ± 5.4) yrs	Vaginal bleeding plus clinical observation of the placenta	*F5 (Arg506Gln)*	Cases: 3/5/19	Yes	*GlnGln* vs. *GlnArg/ArgArg*	na	Yes
		29 controls, matched for age, parity, ethnicity			Controls: 0/1/28		*GlnGln/GlnArg* vs. *ArgArg*	11.8 (1.36–102)	
							GlnGln vs. *GlnArg*	na	
							**Gln* vs. **Arg*	14.5 (1.81–117)	
Kupferminc, 1999[39]	Israel, Jews	20 cases	Clinical criteria	*F5 (Arg506Gln)*	Cases: -/5†/15	Yes	*GlnGln* vs. *GlnArg/ArgArg*	na	Yes
		110 controls, matched for age, ethnicity			Controls: 0/7/103		*GlnGln/GlnArg* vs. *ArgArg*	4.9 (1.37–17.4)	
							GlnGln vs. *GlnArg*	na	
							**Gln* vs. **Arg*	N/A	
				MTHFR (C677T)	Cases: 3/-/17‡	Not	*TT* vs. *TC/CC*	1.98 (0.48–8.06)	N/A
					Controls: 9/-/101‡		*TT/TC* vs. *CC*	N/A	
							TT vs. *TC*	N/A	
							**T* vs. **C*	N/A	
				F2 (G20210A)	Cases: 0/4/16	Yes	*AA* vs. *AG/GG*	na	Yes
					Controls: 0/3/107		*AA/AG* vs. *GG*	8.9 (1.82–43.57)	
							AA vs. *AG*	na	
							**A* vs. **G*	8.03 (1.72–37.4)	
Kupferminc, 2000[40]	Israel, Jews	27 cases	Clinical criteria	*F2 (G20210A)*	Cases: 0/5/22	Yes	*AA* vs. *AG/GG*	na	Yes
		156 controls			Controls: 0/5/151		*AA/AG* vs. *GG*	6.86 (1.83–25.63)	
							AA vs. *AG*	na	
							**A* vs. **G*	6.26 (1.74–22.4)	
Alfirevic, 2001[41]	UK, mixed	23 cases	N/A	*F5 (Arg506Gln)*	Cases: 0/0/23	Not	*GlnGln* vs. *GlnArg/ArgArg*	na	Yes
		44 controls, matched for age, parity, gestation			Controls: 0/3/41		*GlnGln/GlnArg* vs. *ArgArg*	na	
							GlnGln vs. *GlnArg*	na	
							**Gln* vs. **Arg*	na	
				MTHFR (C677T)	Cases: 0/-/23‡	Not	*TT* vs. *TC/CC*	na	N/A
					Controls: 2/-/42‡		*TT/TC* vs. *CC*	N/A	
							TT vs. *TC*	na	
							**T* vs. **C*	N/A	
				F2 (G20210A)	Cases: -/1†/22	Not	*AA* vs. *AG/GG*	N/A	N/A
					Controls: -/2†/42		*AA/AG* vs. *GG*	1.0 (0.08–11.12)	
							AA vs. *AG*	N/A	
							**A* vs. **G*	N/A	
Gebhardt, 2001[42]	South Africa, blacks	18 cases	Clinical criteria plus clinical observation of the placenta	*MTHFR (C677T)*	Cases: 0/5/13	Not	*TT* vs. *TC/CC*	na	Yes
		114 controls			Controls: 2/30/82		*TT/TC* vs. *CC*	0.99 (0.28–3.30)	

(*Continued*)

TABLE 1. (*Continued*)

First Author, Year	Study Area, Ethnicity	Study Population	Placental Abruption Diagnostic Criteria*	Gene (Polymorphism)	Genotype Distribution mtmt/mtwt/wtwt	Showing Association	Comparison	OR (95% CI)	HWE
							TT vs. *TC*	na	
							**T* vs. **C*	0.92 (0.29–2.72)	
				MTHFR (*A1298C*)	Cases: 3/9/6	Yes	*CC* vs. *CA/AA*	4.36 (0.94–20.1)	Yes
					Controls: 5/39/70		*CC/CA* vs. *AA*	3.18 (1.01–10.37)	
							CC vs. *CA*	2.60 (0.52–12.9)	
							**C* vs. **A*	2.61 (1.18–5.77)	
Yoshimura, 2001[43]	Japan, Japanese	35 cases, (31.5 ± 3.7) yrs	Clinical criteria plus clinical observation of the placenta	*NOS3* (*Glu298Asp*)	Cases: 0/14/21	Yes	*AspAsp* vs. *AspGlu/GluGlu*	na	Yes
		170 controls			Controls: 2/22/146		*AspAsp/AspGlu* vs. *GluGlu*	4.06 (1.89–8.71)	
							AspAsp vs. *AspGlu*	na	
							**Asp* vs. **Glu*	3.02 (1.53–5.98)	
Agorastos, 2002[44]	Greece, Greeks	7 cases	Clinical criteria plus clinical observation of the placenta	*F5* (*Arg506Gln*)	Cases: 0/3/4	Yes	*GlnGln* vs. *GlnArg/ArgArg*	na	Yes
		100 controls, matched for ethnicity			Controls: 0/4/96		*GlnGln/GlnArg* vs. *ArgArg*	18 (2.2–159)	
							GlnGln vs. *GlnArg*	na	
							**Gln* vs. **Arg*	13.36 (2.65–67.22)	
				F2 (*G20210A*)	Cases: -/1†/6	Not	*AA* vs. *AG/GG*	N/A	N/A
					Controls: -/2†/98		*AA/AG* vs. *GG*	8.1 (0–149)	
							AA vs. *AG*	N/A	
							**A* vs. **G*	N/A	
Hira, 2002[45]	South Africa, blacks	100 cases	Clinical criteria	*F5* (*Arg506Gln*)	Cases: 0/0/100	Not	*GlnGln* vs. *GlnArg/ArgArg*	na	N/A
		217 controls			Controls: 0/0/217		*GlnGln/GlnArg* vs. *ArgArg*	na	
							GlnGln vs. *GlnArg*	na	
							**Gln* vs. **Arg*	na	
				F2 (*G20210A*)	Cases: 0/0/100	Not	*AA* vs. *AG/GG*	na	N/A
					Controls: 0/0/217		*AA/AG* vs. *GG*	na	
							AA vs. *AG*	na	
							**A* vs. **G*	na	
				THBD (*Ala455Val*)	Cases: 0/0/100	Not	*ValVal* vs. *ValAla/AlaAla*	na	Yes
					Controls: 0/3/214		*ValVal/ValAla* vs. *AlaAla*	na	
							ValVal vs. *ValAla*	na	
							**Val* vs. **Ala*	na	
				MTHFR (*C677T*)					
					Cases: 0/13/87	Not	*TT* vs. *TC/CC*	na	Yes
					Controls: 2/22/193		*TT/TC* vs. *CC*	1.2 (0.58–2.47)	
							TT vs. *TC*	na	
							**T* vs. **C*	1.0 (0.54–2.17)	

(*Continued*)

TABLE 1. (*Continued*)

First Author, Year	Study Area, Ethnicity	Study Population	Placental Abruption Diagnostic Criteria*	Gene (Polymorphism)	Genotype Distribution mtmt/mtwt/wtwt	Showing Association	Comparison	OR (95% CI)	HWE
Facchinetti, 2003[46]	Italy, whites	50 cases, (31.7 ± 5.9) yrs	Clinical criteria plus histological examination of the placenta	*F5 (Arg506Gln)*	Cases: 0/11/39	Yes	*GlnGln* vs. *GlnArg/ArgArg*	na	Yes
		100 controls, matched for age, parity, ethnic background			Controls: 0/3/97		*GlnGln/GlnArg* vs. *ArgArg* *GlnGln* vs. *GlnArg* **Gln* vs. **Arg*	9.12 (2.18–31.7) na 8.11 (2.20–29.80)	
				F2 (G20210A)	Cases: 0/10/40 Controls: 0/2/98	Yes	*AA* vs. *AG/GG* *AA/AG* vs. *GG* *AA* vs. *AG* **A* vs. **G*	na 12.25 (2.36–29.6) na 11 (2.36–51.23)	Yes
Prochazka, 2003[47]	Sweden, whites	102 cases (30.1 [SD 5.6]) yrs	Clinical criteria plus clinical examination of the placenta	*F5 (Arg506Gln)*	Cases: -/16†/86	Not	*GlnGln* vs. *GlnArg/ArgArg*	N/A	N/A
		2371 controls			Controls: -/255†/2116		*GlnGln/GlnArg* vs. *ArgArg* *GlnGln* vs. *GlnArg* **Gln* vs. **Arg*	1.5 (0.9–2.7) N/A N/A	
Jaaskelainen, 2004[48]	Finland, whites	116 cases, (30 [28.9–31.1]) yrs	Clinical criteria plus clinical observation or histological examination of the placenta	*F5 (Met385Thr)*	Cases: 2/12/102	Yes	*ThrThr* vs. *ThrMet/MetMet*	1.90 (0.17–21.8)	Yes
		112 controls			Controls: 1/28/83		*ThrThr/ThrMet* vs. *MetMet* *ThrThr* vs. *ThrMet* **Thr* vs. **Met*	0.40 (0.2–0.8) 4.60 (0.38–56.5) 0.48 (0.25–0.91)	
				F5 (Arg485Lys)	Cases: 0/13/103 Controls: 1/8/103	Not	*LysLys* vs. *LysArg/ArgArg* *LysLys/LysArg* vs. *ArgArg* *LysLys* vs. *LysArg* **Lys* vs. **Arg*	na 1.4 (0.6–3.5) na 1.3 (0.5–2.9)	Yes
				F5 (Arg506Gln)	Cases: 0/3/113 Controls: 0/4/108	Not	*GlnGln* vs. *GlnArg/ArgArg* *GlnGln/GlnArg* vs. *ArgArg* *GlnGln* vs. *GlnArg* **Gln* vs. **Arg*	na 0.7 (0.15–3.28) na 0.7 (0.15–3.25)	Yes
Toivonen, 2004[49]	Finland, whites	117 cases, (30 [28.8–31.1]) yrs	Clinical criteria plus clinical observation or histological examination of the placenta	*EPHX (Tyr113His)*	Cases: 11/44/62	Not	*HisHis* vs. *HisTyr/TyrTyr*	0.64 (0.28–1.45)	Yes
		115 controls			Controls: 16/47/52		*HisHis/HisTyr* vs. *TyrTyr*	0.73 (0.43–1.22)	

(*Continued*)

TABLE 1. (Continued)

First Author, Year	Study Area, Ethnicity	Study Population	Placental Abruption Diagnostic Criteria*	Gene (Polymorphism)	Genotype Distribution mtmt/mtwt/wtwt	Showing Association	Comparison	OR (95% CI)	HWE
							HisHis vs. *HisTyr*	0.73 (0.3–1.75)	
							**His* vs. **Tyr*	0.75 (0.5–1.11)	
				EPHX (*His139Arg*)	Cases: 2/39/76	Not	*ArgArg* vs. *ArgHis/HisHis*	na	Yes
					Controls: 0/33/82		*ArgArg/ArgHis* vs. *HisHis*	1.34 (0.77–2.33)	
							ArgArg vs. *ArgHis*	na	
							**Arg* vs. **His*	1.34 (0.81–2.20)	
Parle-McDermott, 2005[50]	Ireland, whites	62 cases	Clinical criteria or clinical observation of the placenta or a statement in the case records that the patient was a definitive case of placental abruption	*MTHFD1* (*Arg653Gln*)	Cases: 21/23/18	Yes	*GlnGln* vs. *GlnArg/ArgArg*	2.85 (1.47–5.53)	Yes
		184 controls			Controls: 28/96/60		*GlnGln/GlnArg* vs. *ArgArg*	1.18 (0.63–2.21)	
							GlnGln vs. *GlnArg*	3.13 (1.51–6.47)	
							**Gln* vs. **Arg*	1.57 (1.01–2.44)	
				MTHFR (*C677T*)	Cases: 5/31/26	Not	*TT* vs. *TC/CC*	0.64 (0.23–1.76)	Yes
					Controls: 22/80/80		*TT/TC* vs. *CC*	1.0 (0.6–1.94)	
							TT vs. *TC*	0.58 (0.2–1.68)	
							**T* vs. **C*	0.96 (0.63–1.44)	
				MTHFR (*A1298C*)	Cases: 6/31/25	Not	*CC* vs. *CA/AA*	0.98 (0.37–2.61)	Yes
					Controls: 18/75/91		*CC/CA* vs. *AA*	1.45 (0.81–2.6)	
							CC vs. *CA*	0.80 (0.29–2.22)	
							**C* vs. **A*	1.23 (0.81–1.86)	
Toivonen, 2005[51]	Finland, whites	116 cases, (30 [28.9–31.1]) yrs	Clinical criteria plus clinical observation or histological examination of the placenta	*NOS3* (*Glu298Asp*)	Cases: 16/45/55	Not	*AspAsp* vs. *AspGlu/GluGlu*	1.34 (0.60–2.99)	Yes
		113 controls			Controls: 12/48/53		*AspAsp/AspGlu* vs. *GluGlu*	0.97 (0.58–1.64)	
							AspAsp vs. *AspGlu*	1.42 (0.60–3.33)	
							**Asp* vs. **Glu*	1.06 (0.72–1.57)	
Hillermann, 2005[52]	South Africa, blacks	50 cases, (28 [16–42]) yrs	Clinical criteria plus clinical observation of the placenta	*NOS3* (*Glu298Asp*)	Cases: 2/21/24	Yes	*AspAsp* vs. *AspGlu/GluGlu*	1.82 (0.16–20.85)	Yes

(Continued)

TABLE 1. (*Continued*)

First Author, Year	Study Area, Ethnicity	Study Population	Placental Abruption Diagnostic Criteria*	Gene (Polymorphism)	Genotype Distribution mtmt/mtwt/wtwt	Showing Association	Comparison	OR (95% CI)	HWE
		50 controls			Controls: 1/8/33		*AspAsp/AspGlu* vs. *GluGlu*	3.51 (1.76–9.98)	
							AspAsp vs. *AspGlu*	0.76 (0.06–9.61)	
							**Asp* vs. **Glu*	2.49 (1.04–6.07)	
				AGT (Met235Thr)	Cases: 32/12/4 Controls: 31/12/2	Not	*ThrThr* vs. *ThrMet/MetMet*	0.9 (0.37–2.16)	Yes
							ThrThr/ThrMet vs. *MetMet*	0.5 (0.09–2.94)	
							ThrThr vs. *ThrMet*	1.03 (0.40–2.64)	
							**Thr* vs. **Met*	0.82 (0.39–1.70)	
Dizon-Townson, 2005[53]	USA, mixed	31 cases	Clinical criteria or histological examination of the placenta	*F5 (Arg506Gln)*	Cases: 0/0/31	Not	*GlnGln* vs. *GlnArg/ArgArg*	na	Yes
		4436 controls			Controls: 0/121/4315		*GlnGln/GlnArg* vs. *ArgArg*	na	
							GlnGln vs. *GlnArg*	na	
							**Gln* vs. **Arg*	na	
Jaaskelainen, 2006[54]	Finland, whites	117 cases, (30 [28.9–31.1]) yrs	Clinical criteria plus clinical observation or histological examination of the placenta	*MTHFR (C677T)*	Cases: 6/36/75	Not	*TT* vs. *TC/CC*	0.96 (0.30–3.05)	Yes
		112 controls			Controls: 6/42/64		*TT/TC* vs. *CC*	0.74 (0.43–1.27)	
							TT vs. *TC*	1.16 (0.34–3.93)	
							**T* vs. **C*	0.81 (0.52–1.26)	
Zhang, 2006[55]	USA, mixed	62 cases, (26.65 ± 6.6)	Clinical criteria plus histological examination of the placenta	*AGT (Met235Thr)*	Cases: 26/27/9	Yes	*ThrThr* vs. *ThrMet/MetMet*	3.30 (1.81–6.04)	No
		240 controls			Controls: 43/95/102		*ThrThr/ThrMet* vs. *MetMet*	4.35 (2.05–9.22)	
							ThrThr vs. *ThrMet*	2.12 (1.11–4.06)	
							**Thr* vs. **Met*	2.90 (1.92–4.36)	
Naidu, 2006[56]	South Africa, blacks	155 cases, (27 [13–44])	Clinical criteria plus sonographic diagnosis plus clinical observation of the placenta	*MTHFR (C677T)*	Cases: 1/21/133	Not	*TT* vs. *TC/CC*	1.09 (0.09–12.12)	Yes
		338 controls			Controls: 2/38/298		*TT/TC* vs. *CC*	1.23 (0.70–2.15)	
							TT vs. *TC*	0.90 (0.07–10.57)	
							**T* vs. **C*	1.20 (0.71–2.04)	

(*Continued*)

TABLE 1. (*Continued*)

First Author, Year	Study Area, Ethnicity	Study Population	Placental Abruption Diagnostic Criteria*	Gene (Polymorphism)	Genotype Distribution mtmt/mtwt/wtwt	Showing Association	Comparison	OR (95% CI)	HWE
Jarvenpaa, 2006[57]	Finland, whites	9 cases, 111 controls	Clinical criteria	*F5 (Arg506Gln)*	Cases: 0/2/7	Yes	*GlnGln* vs. *GlnArg/ArgArg*	na	Yes
					Controls: 0/2/109		*GlnGln/GlnArg* vs. *ArgArg*	15.57 (1.9–127)	
							GlnGln vs. *GlnArg*	na	
							**Gln* vs. **Arg*	13.75 (1.81–104)	
				F2 (G20210A)	Cases: 0/0/9	Not	*AA* vs. *AG/GG*	na	Yes
					Controls: 0/1/110		*AA/AG* vs. *GG*	na	
							AA vs. *AG*	na	
							**A* vs. **G*	na	
				MTHFR (C677T)	Cases: 1/-/8‡	Not	*TT* vs. *TC/CC*	2.65 (0.27–25.5)	N/A
					Controls: 5/-/106‡		*TT/TC* vs. *CC*	N/A	
							TT vs. *TC*	N/A	
							**T* vs. **C*	N/A	
Ananth, 2007[58]	USA, mixed	196 cases	Clinical criteria or clinical observation of the placenta or sonographic diagnosis	*MTRR (A66G)*	Cases: 42/76/78	Not	*GG* vs. *GA/AA*	1.06 (0.65–1.73)	Yes
		191 controls matched for parity, race/ethnicity			Controls: 39/83/69		*GG/GA* vs. *AA*	0.85 (0.56–1.29)	
							GG vs. *GA*	1.17 (0.68–2.0)	
							**G* vs. **A*	0.85 (0.63–1.13)	
				BHMT (G742A)	Cases: 25/83/88	Not	*AA* vs. *AG/GG*	1.49 (0.78–2.87)	Yes
					Controls: 17/87/87		*AA/AG* vs. *GG*	1.02 (0.68–1.53)	
							AA vs. *AG*	1.54 (0.77–3.05)	
							**A* vs. **G*	1.08 (0.8–1.46)	
Ananth, 2007[59]	USA, mixed	195 cases, 189 controls matched for parity, race/ethnicity	Clinical criteria or clinical observation of the placenta or sonographic diagnosis	*MTHFR (C677T)*	Cases: 26/69/100	Not	*TT* vs. *TC/CC*	0.72 (0.41–1.27)	No
					Controls: 33/69/87		*TT/TC* vs. *CC*	0.81 (0.54–1.21)	
							TT vs. *TC*	0.78 (0.42–1.45)	
							**T* vs. **C*	0.81 (0.60–1.10)	
				MTHFR (A1298C)	Cases: 16/62/187	Not	*CC* vs. *CA/AA*	2.32 (0.93–5.78)	Yes
					Controls: 7/64/118		*CC/CA* vs. *AA*	1.10 (0.73–1.67)	
							CC vs. *CA*	2.36 (0.91–6.12)	
							**C* vs. **A*	1.22 (0.86–1.71)	

*Diagnostic criteria for placental abruption: (1) Clinical criteria: vaginal bleeding, uterine tenderness and fetal distress, (2) Clinical observation of the placenta, (3) Histological examination of the placenta, (4) Sonographic diagnosis.

†Data presented as mtwt + mtmt.

‡Data presented as wtwt + mtwt.

HWE indicates Hardy-Weinberg Equilibrium; N/A, not available; na, nonapplicable.

TABLE 2. Genetic Polymorphisms Investigated in Relation to Placental Abruption Risk

dbSNP* rs Number	Gene	Chromosomal Position	Base Change†	Average Heterozygosity (SE)	Amino Acid Change‡	Detection Method Used by the Individual Studies	Functional Effect
rs1801133	*MTHFR*	1p36.22	Exon 5: *C677T*	0.412 (0.190)	*Ala222Val*	RFLPs- creates a *Hinf*I site[39,41,42,45,50,54,56,59] SSOP[57]	Heterozygous and homozygous carriers of the 677T allele variant have a 30%–40% and 60%–70% reduced enzyme activity, respectively, as determined by in vitro analysis of the MTHFR activity[60]
rs1801131	*MTHFR*	1p36.22	Exon 5: *A1298C*	0.340 (0.233)	*Glu429Ala*	RFLPs- creates a *Mbo*II site[42,59] SSOP[50]	Homozygous carriers have 30–40% reduction of the enzyme activity[61]
rs2236225	*MTHFD1*	14q23.2	Exon 20: *G1958A*	0.419 (0.189)	*Arg653Gln*	RFLPs- creates a *Msp*I site[50]	Unknown, replacement of a cross-kingdom conservated amino acid[62]
rs1801394	*MTRR*	5p15.3-p15.2	Exon 2: *A66G*	0.489 (0.074)	*Ile22Met*	RFLPs- creates a *Nsp*I site[58]	Unknown
rs3733890	*BHMT*	5q13.1-q15	Exon 6: *G742A*	0.395 (N/A)	*Arg239Gln*	RFLPs- creates a *Hinf*I site[58]	Unknown, may result in elevated homocysteine levels[58]
rs6025	*F5*	1q24.2	Exon 10: *G1691A*	0.008 (0.062)	*Arg506Gln*	RFLPs- loss of a *Mnl*I site[38,39,41,44,46] N/A[47] SSOP[45,48,53,57]	Failure of activated protein C (APC) to recognize a cleavage site on factor V, resistance to APC degradation[63]
rs6020	*F5*	1q24.2	Exon 10: *G1628A*	0.446 (0.155)	*Arg485Lys*	RFLPs- loss of a *Alw26*I site[48]	Unknown
rs6033	*F5*	1q24.2	Exon 8: *T1335C*	N/A	*Met385Thr*	RFLPs- creates a *Rsa*I site[48]	Unknown
rs1799963	*F2*	11p11.2	3′-utr: *G20210A*	N/A	No	RFLPs- a *Hind* III site[39,40,41,44-46] SSOP[57]	Higher plasma prothrombin levels[64]
rs1042579	*THBD*	20p11.21	Exon 1: *C1418T*	0.191 (0.243)	*Ala455Val*	SSOP[45]	Unknown
rs1799983	*NOS3*	7q36.1	Exon 7: *G894T*	0.289 (0.247)	*Glu298Asp*	RFLPs- loss of a *Ban*II site[43,51,52]	Vulnerability to enzymatic cleavage[65]
rs699	*AGT*	1q42-43	Exon 2: *C704T*	0.469 (0.121)	*Met235Thr*	RFLPs- creates a *Asp*I site[52] SSOP[55]	Increased AGT levels[66,67]
rs1051740	*EPHX1*	1q42.12	Exon 3: *T612C*	0.442 (0.161)	*Tyr113His*	RFLPs- creates a *Tth*111 I site[49]	Decreases enzyme activity by 40%[68]
rs2234922	*EPHX1*	1q42.12	Exon 4: *A691G*	0.324 (0.239)	*His139Arg*	RFLPs- creates a *Rsa* I site[49]	Increases enzyme activity by 25%[68]

*Database of single nucleotide polymorphisms (dbSNP). Bethesda (MD): National Center for Biotechnology Information, National Library of Medicine (dbSNP Build ID: 126). Available at: http://www.ncbi.nlm.nih.gov/SNP/.
†Base change symbolized as: locus: wild-type allele, nucleotide position, mutant allele. 3′-utr: 3′ untranslated region.
‡Amino acid substitution for nonsynonymous polymorphisms symbolized as: wild-type amino acid (3-letter coding), amino acid position, mutant amino acid (3-letter coding). RFLPs indicates restriction fragment length polymorphisms; SSOP, sequence-specific oligonucleotide probing; NA, not available.

single nucleotide polymorphisms (dbSNP),[76] the chromosomal gene position, the nucleotide base change, the average heterozygosity, and the amino acid substitution for each polymorphism.

Thrombophilia

Numerous studies have explored associations between abruption and thrombophilias.[4] Methylenetetrahydrofolate reductase (MTHFR) catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the primary form of serum folate. Nine case-control studies[39,41,42,45,50,54,56,57,59] have investigated the association of the C-to-T mutation at nucleotide position 677 of the *MTHFR* gene[60] with placental abruption. None has found an association, regardless of the ethnicity of the population. An additional polymorphism of the *MTHFR* gene, *A1298C*,[61] has been genotyped by 3 case-control studies.[42,50,59] A positive association was found by only

TABLE 3. Random Effects and Fixed Effects Odds Ratios With the Corresponding 95% Confidence Intervals and Heterogeneity Tests Results (I^2, Q-Test) for the Dominant Model for the Minor Allele of *FV* Leiden *R506Q*, *FII G20210A*, *MTHFR C677T*, *MTHFR A1298C*, *eNOS G894T*, and *AGT C704T* Polymorphisms in Association to Placental Abruption

Polymorphism	Population	Studies	Fixed Effects OR (95% CI)	Random Effects OR (95% CI)	I^2 (%)	*P* Q-test
FV Leiden *R506Q*						
Dominant model for allele Q	All	10	2.35 (1.62–3.41)	3.42 (1.42–8.25)	66	<0.01
	Whites	5	2.47 (1.47–3.43)	4.21 (1.26–14.10)	76	<0.01
FII G20210A						
Dominant model for allele A	All	7	6.67 (3.21–13.88)	6.82 (3.23–14.37)	0	0.66
	Whites	3	10.37 (2.99–35.96)	9.45 (2.76–32.42)	0	0.81
MTHFR C677T						
Dominant model for allele C	All	9	1.24 (0.83–1.85)	1.20 (0.80–1.80)	0	0.89
	Whites	3	1.21 (0.59–2.48)	1.16 (0.56–2.39)	0	0.52
	Blacks	3	1.22 (0.25–6.00)	1.16 (0.23–5.76)	0	0.87
MTHFR A1298C						
Dominant model for allele C	All	3	1.33 (0.97–1.83)	1.44 (0.90–2.31)	43	0.18
ENOS G894T						
Dominant model for allele T	All	3	1.69 (1.15–2.50)	2.30 (0.84–6.31)	82	<0.01
AGT C704T						
Dominant model for allele T	All	2	3.16 (1.65–6.04)	1.74 (0.22–13.86)	na	0.03

na indicates nonapplicable.

one.[42] In this South African "colored" population, the ORs for the allele contrast and the dominant model were 2.6 (95% CI = 1.2–5.8) and 3.2 (1.0–10), respectively. In the same study, combined heterozygosity for mutations *C677T* and *A1298C* was found in 22% of the abruption cases, providing an OR of 5.1 (1.1–24). The meta-analysis for the *MTHFR C677T* polymorphism showed lack of heterogeneity, overall ($P = 0.89$, $I^2 = 0$), in whites ($P = 0.52$, $I^2 = 0$) and in blacks ($P = 0.87$, $I^2 = 0$). The respective fixed-effect ORs for the dominant model were 1.2 (0.83–1.9), 1.2 (0.59–2.5) and 1.2 (0.25–6.0) (Table 3). The meta-analysis of the 3 studies[42,50,59] for the *MTHFR A1298C* polymorphism showed signs of heterogeneity ($P = 0.18$, $I^2 = 43$) and lack of association for the dominant model, with the fixed-effect OR = 1.3(0.97–1.8) and the random-effect OR = 1.4 (0.90–2.31) (Table 3).

MTHFD1 is a trifunctional enzyme (5,10-methylenetetrahydrofolate dehydrogenase; 5,10-methenyltetrahydrofolate cyclohydrolase; and 10-formyltetrahydrofolate synthetase) involved in folate metabolism. A nonsynonymous SNP of the *MTHFD1* gene, designated as *Arg653Gln*[62] was investigated by Parle-McDermott et al.[50] The estimated ORs under the allele contrast and the recessive model were 1.6 (1.0–2.4) and 2.9 (1.5–5.5), respectively.

Three nonsynonymous SNPs of the factor V gene (*F5*), (*Arg506Gln*,[63,77] *Met385Thr,* and *Arg485Lys*) have been studied for their potential role in placental abruption risk. Ten case-control studies[38,39,41,44–48,53,57] have assessed *Arg506Gln* (Leiden mutation), with a positive association in 5.[38,39,44,46,57] Jaaskelainen et al[48] genotyped all 3 F5 polymorphisms, with only the *Met385Thr* polymorphism associated with abruption under the dominant and the allele contrast model, [ORs = 0.4 (0.2–0.8) and 0.5(0.25–0.91]. The frequency of the haplotype encoding the *Thr385-Arg485-Arg506* variant was lower in the patient than in the control group, giving an OR of 0.52 (0.27–0.99). A meta-analysis of the 10 published studies for the *Arg506Gln* polymorphism demonstrated high heterogeneity, overall ($P < 0.01$, $I^2 = 66$) and among white women ($P < 0.01$, $I^2 = 76$). There was a positive association under the dominant model, with the respective random-effects ORs equal to 3.4 (1.4–8.3) and 4.2 (1.3–14) (Table 3).

Factor II (prothrombin) is a coagulation factor that it is transformed into thrombin after its activation by prothrombinase complex at the site of vascular injury.[78] Seven case-control studies of abruption[39–41,44–46,57] have evaluated a guanine-to-adenine substitution at position 20210 (*G20210A*)[64] of the prothrombin gene (*F2*); 3[39,40,46] showed associations. The meta-analysis for the *G20210A* polymorphism showed lack of heterogeneity, and a positive association under the dominant model; fixed-effects ORs were 6.7 (3.2–13) overall and 10 (3.0–36) among white women (Table 3).

Thrombomodulin is an endothelial transmembrane glycoprotein that converts the activity of thrombin from procoagulant to anticoagulant; variants have been associated with thrombotic disorders.[79,80]A nonsynonymous SNP (*Ala455Val*) of the thrombomodulin gene (*THBD*) was investigated in relation to placental abruption by Hira et al[45] in black South African women. No association was found, although only 3 heterozygous were found in the control cohort and none in the patient group.

Methionine synthase reductase (MTRR) and betaine-homocysteine S-methyltransferase (BHMT) regulate homocysteine metabolism. A study by Ananth et al[58] focused on 2 variants of these enzymes, *MTRR* (*A66G*) and *BHMT* (*G742A*),[81,82] with no associations observed. After adjusting for confounders, a positive association emerged for *BHMT* (*G742A*) polymorphism, with an OR of 2.8 (1.8–5.0) for AA versus GG.

Hemodynamics

Hemodynamic changes in pregnancy play an important role in the development of placental abruption.[6,83,84] Endothelial nitric oxide synthase (NOS3) regulates endothelial nitric oxide availability, which in turn facilitates pregnancy-related vasodilatation.[85–87] A nonsynonymous functional SNP of theNOS3 gene (*NOS3*) designated as *Glu298Asp*[65,88] was genotyped in 3 studies.[43,51,52] Two (1 in Japanese women[43] and 1 in South African black women[52]) reported a positive association, with ORs under the dominant model of 4.1 (1.9–8.7) and 3.5 (1.8–10), respectively. A third study, by Toivonen et al[51] found no association. A meta-analysis of the 3 studies showed a high degree of heterogeneity ($P < 0.01$, $I^2 = 82$); in a dominant model, the random-effects OR was 2.3 (0.84–6.3) (Table 3).

Angiotensinogen (AGT) is the precursor of the hormone angiotensin II. One functional variant of the *AGT* gene, the nonsynonymous SNP *Met235Thr*,[66,67] has been investigated by 2 case-control studies.[52,55] Zhang et al[55] reported an OR under the recessive model of 3.3 (1.8–6.0). A high level of heterogeneity ($P = 0.03$) was observed in the meta-analysis of the 2 studies, with little evidence of an association under the dominant model, [random-effects OR = 1.7 (0.22–14)] (Table 3).

Oxidative Stress

Genes involved in oxidative stress, such as microsomal epoxide hydrolase gene (*EPHX*), may play a role in the development of pathologic processes in the placenta.[49] Two functional nonsynonymous SNPs of *EPHX* gene (*Tyr113His* and *His139Arg*)[68] have been analyzed in a study from Finland.[49] Single-point allele and genotype distributions for both polymorphisms were not statistically different between the groups. A single haplotype association analysis showed a lower risk of abruption with the low activity haplotype (*His113-His139*) (0.55 [0.36–0.85]).

Interactions

As with other complex traits, the development of placental abruption is likely to be affected by several genes that act collectively, with allelic variants at different genes having either additive or contrasting effects.[75] There are many possible interactions among genetic polymorphisms and possible effect modifiers such as maternal age and parity, race, cigarette smoking, nutrition, prenatal care, or other environmental factors.

Gene-Gene Interactions

Two studies[50,58] investigated possible gene-gene interactions. Parle-McDermott et al[50] performed a combined analysis of *MTHFR C677T* and *MTHFD1 Arg653Gln* polymorphisms by the nonhierarchical logistic model analysis, with no significant effects observed (data not available).

Ananth et al[58] examined a potential synergistic effect between *MTRR A66G* and *BHMT G742A* polymorphisms. Homozygotes for the *BHMT* mutant allele (A/A) were associated with increased risk for abruption with the wild type (A/A) and heterozygous (A/G) forms of the *MTRR* polymorphism [adjusted ORs = 4.8 (1.2–19) and 2.4 (1.0–8.4), respectively].

Gene-Environment Interactions

Conflicting results among studies investigating genetic polymorphisms and the risk of placental abruption may be due to lack of information on the possible interactions with environmental factors. Differences in total homocysteine, folate, and vitamin B_{12} concentrations between cases and controls were examined by genotypes of *MTRR A66G* and *BHMT G742A* polymorphisms by Ananth et al.[58] Among women carrying the wild-type form of *MTRR (A/A)*, homocysteine concentrations were lower in cases than controls ($P = 0.011$), whereas cases carrying the wild-type and heterozygous mutant form of *BHMT* (*G/G* and *G/A*) had higher levels of homocysteine ($P = 0.031$ and $P < 0.001$, respectively).

Ananth et al[59] compared the distributions of plasma total homocysteine, folate, and vitamin B_{12} between cases and controls within the different genotypes of *MTHFR C677T* and *MTHFR A1298C* mutations. Elevated homocysteine and B_{12} concentrations were reported in cases compared with controls among women with the wild-type genotype of *MTHFR C677T* ($P = 0.039$ for homocysteine, and $P = 0.048$ for B_{12}).

DISCUSSION

Genetic association studies in placental abruption have been inconsistent. The complex nature of the disease implies that for individual polymorphisms, associations are likely to be modest. To detect such modest genetic effects, stronger study designs will be necessary.

Power Improvement

Placental abruption is a relatively rare pregnancy complication, occurring in only 0.5% to 1% of pregnancies.[89] Past studies have been relatively small. Small studies often lack adequate representation in certain genotype groups, are unable to address gene-gene or gene-environment interactions, and are subject to publication bias.[69] Larger samples would improve power; selection of cases that are genetically loaded may also aid power. The genetic component is thought to be more prominent in recurrent cases.[27] Therefore, by selecting cases with a strong family history, cases may be weighted toward individuals whose disease has a strong genetic etiology.[90]

Stratification

Lack of stratification in genetic association studies might blur the genetic effect. On the other hand, there is concern about the possible effects of population stratification in case-control studies.[91] Unequal genetic admixture in the control and patient populations can result in spurious associations. One approach to minimize this problem is to measure and adjust for genetic markers that are not linked to the disease under investigation.[92] Furthermore, since the prevalence of polymorphisms can vary widely across populations, stratification on ethnicity in studies with mixed populations, could help to unmask a true genetic effect.

Definition Criteria

Variability in the diagnostic criteria for placental abruption might contribute to the heterogeneity of the results. In most studies presented here, the diagnosis of abruption was a clinical one, which was then confirmed by antepartum ultrasonographic diagnosis, histologic examination, or observation of a retroplacental blood clot after delivery. Placental abruption was defined only on the basis of clinical diagnosis alone in 4 studies,[39,40,45,57] and in 1 study[41] diagnostic information was not provided.

Hardy-Weinberg Equilibrium and Genotyping

The lack of Hardy-Weinberg equilibrium among controls[55,59] suggests genotyping errors, population stratification, or selection bias,[93,94] as well as continued selection, migration, mutation, or absence of random mating.[95,96] The possible lack of masking of genotyping personnel in 19 studies[38–52,54–57] could also be a source of bias.

Candidate Gene Selection

Genomic or proteomic expression analyses can assist in the selection of candidate variants by ranking those genes that appear to be the most active in the disease process. This overlapping of independent sources of information has been termed "genomic convergence" and is expected to provide new insights into the cellular mechanisms involved in placental dysfunction.[97,98]

Maternal-Fetal Interaction

Because placenta is a fetal tissue, fetal genetic variants may also play a role in abruption. Family designs may be particularly useful tools in studying the effects of maternal and fetal genes on the risk of placental abruption. Moreover, family-based designs are robust against population substructure, and associations imply both linkage and association.[99] Only 1 study has evaluated the impact of both maternal and fetal genotype on the risk of abruption,[53] without showing a significant association between fetal factor V (Leiden) and the disease. No family-based studies have been conducted.

Gene-Environment Interactions Must be Addressed

Many environmental factors have been associated with increased risk of placental abruption. These factors include gestational hypertensive disease, maternal age and parity, multiple gestations, chorioamnionitis, cocaine and tobacco use.[1] Despite difficulties in study design and assessment of the exposures, such parameters should be incorporated in future studies.[100]

Gene-Gene Interactions

The search for susceptibility loci has been complicated by the increasing number of contributing loci and susceptibility alleles.[101] Elucidating the pathogenesis of the disorder will require simultaneous investigation of many genetic variants of genes that participate in distinct pathophysiological pathways.[102]

The Need for Large-Scale Genetic Association Studies and Meta-Analyses

The overall frequency of placental abruption is low in the population, which makes it more difficult to recruit large numbers of twins, sib pairs, or pedigrees of women who have already experienced placental abruption. Elucidating the genetics of abruption relies largely upon rigorous genetic association studies. Future studies should be planned with the intention of combining them with other similar studies in meta-analyses.[103] The opportunities offered by meta-analysis are the enhancement of power, the ability to place each study in the context of others, (particularly early fake-positive results),[104,105] and the possibility of examining the reasons why studies reach different conclusions.[93,96]

Given the underlying thrombotic phenomena of abruption, it is logical that mutations in genes coding for blood coagulation factors might influence the disease, either by the synthesis of a defective protein or by the enhanced production of a procoagulant protein. The former mechanism is exemplified by the factor V gene *Arg506Gln* SNP, which renders factor V resistant to activated protein C degradation.[63] The latter is exemplified by the prothrombin gene *G20210A* SNP, which alters mRNA stability, resulting in higher prothrombin levels.[64] By utilizing the linkage disequilibrium data from the HapMap Project, these polymorphisms can be investigated in the context of disease-associated haplotypes, to provide further insights about the role of genetic variation in these candidate genes.[106] Moreover, interactions with other candidate genes involved in the thrombophilic pathway or with environmental factors should be investigated. The concomitant study of fetal DNA or fetal-maternal genetic interaction could provide an alternative avenue of research.[53] Finally, a hypothesis-free approach under a genome-wide association study for placental abruption could highlight novel genetic risk factors.[107–109]

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